Evidenced Based Treatment Recommendations for the Treatment of HCV Genotype 1

T. K. Elsethagen

Washington State University

Spring Semester 2012

To the Faculty of Washington State University:

The members of the Committee appointed to examine the master's project of T. K.

Elsethagen find it satisfactory and recommend that it be accepted.

_____

Chair

_____

_____

Abstract

The blood borne infectious disease hepatitis C was initially recognized in the mid- 20th century. It was termed as non-A non-B hepatitis in the 1970's while scientists worked to find and map out its' unique structure. It was isolated and identified in the 1980's and treated initially with interferon alfa in 1986. Since the first mono-therapy of interferon alfa, there have been increasingly more effective therapies and more knowledge created for and about this virus. The objective of this paper is to discuss recent changes to the standard of care for Hepatitis C genotype 1 based on evidence from two newly released drugs: beceprevir and telaprevir.

Evidence Based Treatment Recommendations for the Treatment of HCV genotype 1

Introduction

Hepatitis C is a world-wide infectious disease with six major genotypes. Genotype 1 is the most common in the United States and Western Europe, and is the genotype which boceprevir and telaprevir target. The world-wide infection rate is estimated by The World Health Organization at a minimum of 3% of the worlds' population (Sharma, 2010).

HCV is the most common blood borne infectious disease in the United States with an estimated 3 to 4 million people infected (Dipiro, Talbert, Yee, Matzke, Wells, Posey, 2008). The most common mode of transmission is intravenous drug use, however, those who received blood products prior to screening tests in 1992 are also at greater risk, as are health care workers, incarcerated individuals and hemodialysis patients.

The numbers of those newly infected have dropped off from 200,000 per year in the late 1980's to 20,000 persons in the year 2005. However, because of the slow progression of damage from the HCV infection, those infected 20 to 30 years ago are now in need of health care related to liver disease (Dipiro et al. 2008).

The hepatitis C virus targets the cells of the liver, causing apoptosis and inflammation of these tissues. The natural course of the disease is heterogenous as not all patients will progress to liver disease. However, for most patients HCV will not clear the body and will commonly manifest slowly over decades as liver disease. Of those acutely infected with HCV, 85% go on to a chronic infection. Of those chronically infected, approximately 70% go on to develop cirrhosis, liver failure or hepatocellular cancer (Ashfaq, Javed, Rehman, Nawaz and Riazuddin, 2011).

HCV is a single stranded, enveloped RNA virus of the family flaviviridae. It exhibits an extremely wide genetic heterogeneity both within and across genotypes which is credited to a high replication rate and an error prone replication process. This, unfortunately, leads to a diversity that includes resistant variants and makes the development of anti-virals a challenge (Wyles, 2010).

Diagnosis of HCV is made by laboratory tests. The first test ordered is an enzyme immunoassay (EIA) followed by nucleic acid amplification for confirmation of a positive EIA. A positive EIA identifies antibodies and indicates exposure to the virus. A positive nucleic acid amplification result indicates the presence of active infection (Pearlman, 2011). It can take up to 12 months for the individual to create antibodies to HCV, however, most people will develop antibodies within weeks to months of exposure (Aberg, Goldman, Gray, Long, 2006). After confirmation of active infection, testing is done to determine genotype as this will guide treatment decisions. Genotype 1, the most common type in the United States, is also the hardest to treat and the genotype of focus in this paper.

There is currently no vaccination for hepatitis C because of the high degree of strain variation, but there have been recent advances in HCV research that should further the development of a vaccination (Ashfaq et al. 2011).

There have been, in 2011, important changes to the standard of care for HCV genotype 1. These changes are due to the introduction of two new direct acting anti-virals both approved in May of 2011: boceprevir and teleprevir. These are protease inhibitors that have been shown to significantly increase the number of patients who achieve a sustained virologic response (SVR), or undetectable HCV RNA at 24 weeks after the end of treatment (Ghaney, Nelson, Strader, Thomas, Seeff, 2011). Prior to 2011, SVR rates for HCV genotype 1 were in the 40 to 50 %

range, however, with the addition of boceprevir and telaprevir to the current standard of care, SVR rates are now 70 to 80 % overall (Patel, Pauli and Abdelghany, 2011). The current standard of care (SOC) is a combination therapy of ribaviron (RBV) and pegylated interferon alfa (PEG-INF) for either 24 weeks for genotypes 2 and 3; or 48 weeks for genotype 1 (Ghaney et al. 2011).

Boceprevir and telaprevir were shown to provide these better cure rates with less viral resistance in genotype 1 patients only when given in combination with the SOC, but not as mono-therapy or with PEG-INF alone (Tai and Chung, 2011). When given as mono-therapy, the rate of viral replication dropped off significantly. However, mutation rates and resistance rapidly developed (Kieffer et al. 2007).

The FDA requires boceprevir and teleprevir to be given as combination therapy with ribavirin and pegylated interferon alfa for the treatment of HCV genotype 1 in adult patients (over 18 years) with compensated liver disease, including cirrhosis, who are either treatment naïve or treatment failure (Patel et al. 2011).

Literature Review

Pub Med and CINAHL data bases were used in the literature search (2005- 2011). The terms hepatitis C virus, interferon, ribavirin, telaprevir and boceprevir were used. References from selected articles were used to identify other pertinent citations. One hundred twenty articles were reviewed and twenty-three were chosen for inclusion based on their relevance.

History of Hepatitis C Treatment

Interferons are a group of naturally occurring proteins manufactured within the body. They are a part of a larger group of endogenous proteins called cytokines. There are several types of interferons; alfa and beta are the ones used to treat HCV. These proteins are a part of the host immune system and a part of the bodies' response to invading pathogens or cancer cells.

Synthetic interferon was first introduced as therapy for HCV in 1986 (Feld and Hoofnagle, 2005). The mechanism of action of interferon alfa in the treatment of hepatitis C is not completely understood, however, it is directly anti-viral and may have effects upon cytokine cascades (Sanjiv, 2011). Initially, interferon alfa was given as mono-therapy. Unfortunately, this had limited success with only 6 to 12% of patients maintaining a non-detectable viral load of HCV, or a sustained virologic response rate (SVR) six months after a course of treatment (Feld and Hofnagle, 2005). The SVR rates would improve years later, after the introduction of the anti-viral drug ribavirin, and the modification of interferon-alfa into the longer acting pegylated interferon-alfa.

Ribavirin is a synthetic chemical created in the early 1970's. It was found to have broad spectrum antiviral properties and was initially developed to treat Respiratory Syncytial Virus (Feld and Hoofnagle, 2005). Ribavirins' mechanism of action includes inhibiting viral protein synthesis, thus preventing viral replication (Turkoski, Lance and Tomsik, 2009). It was not until 1998 that ribavirin was given in conjunction with interferon alpha to HCV patients. This combination of interferon alfa with ribavirin improved the HCV patients' SVR rate up to 35 – 40%.

Pegylated interferon consists of the interferon protein changed through a pegylation process whereby a large molecule is attached to the interferon. The molecule attached to interferon is a polyethylene glycol (PEG). Adding this large molecule to the interferon protein enables it to stay active in the body longer. Interferon with a longer half- life was found to be significantly more effective in the treatment of HCV (Feld and Hofnagle, 2005).

Pegylated interferon was introduced as therapy for HCV in 2001 to be given in conjunction with ribavirin. This combination therapy became the standard of care for chronic HCV until recently. Pegylated interferon / ribavirin raised the SVR rates up to as high as 54-56% (Feld and Hofnagle, 2005). However, multiple drug interactions and common side effects such as hemolytic anemia, fatigue, depression, anxiety and neutropenia for ribavirin; depression, rash, influenza-like symptoms, nausea and vomiting for interferon. Also, SVR rates left approximately half of all chronic HCV patients without a cure after treatment.

In 2011, both boceprevir and telaprevir were approved for treatment of HCV when given with pegylated interferon and ribavirin. These protease inhibitors have similar antiviral activity; targeting and bonding to the non-structural (NS) protein: NS3/4 serine protease complex of the HCV genotype 1. The function of this complex is essential for viral polyprotein processing, RNA replication and virion formation of HCV (Morikawa et al. 2011).

Telaprevir

Telaprevir (TPV), for HCV genotype 1, has been studied as mono-therapy and in combination with peginterferon alfa (PEG-INF) and ribavirin (RBV).

A phase Ib, placebo controlled and randomized study of telaprevir as monotherapy for 14 days looked at drug dosing and HCV RNA levels. Rapid emergence of viral resistance to TPV was found, as well as marked declines in HCV RNA wild type, or standard gene form, levels (Kieffer et al. 2007). However, these rapidly occurring mutations with resistance to TPV may still remain sensitive to the broad anti-viral actions of interferon. Because of this outcome, later trials used combinations of TPV always in conjunction with interferon (Tai & Chung). In later TPV phase II trials (PROVE 1, PROVE 2 and PROVE 3) combination therapies with differing lengths of treatment and different populations were studied in the treatment of HCV gentotype 1.

The PROVE 1 trial (n=263) analyzed TPV given to treatment naïve patients for 12 weeks in combination with PEG-IFN and RBV which were given for either 12, 24 or 48 weeks. There was also a control group which received the SOC: RBV and PEG-IFN for 48 weeks with a placebo for the first 12 weeks in place of TPV. The results showed an SVR rate of 61 and 67% in the TPV/PEG-INF/RBV combination groups where the RBV and PEG-IFN were given for 24 and 48 weeks respectively. This is in comparison to the control group which had an SVR rate of 41%. Therapy discontinuation for the TPV arms was 11% vs. 3% in the control group and was related to rash, nausea, vomiting and anemia complications (Lang, 2007).

The phase II study, PROVE 2 was a randomized, partially double-blind and placebo controlled trial of 334 treatment naïve patients with HCV genotype 1(Hezode et al. 2009). There were four arms in this study:

1. A control group: 48 weeks of RBV /PEG-INF alfa-2a: SVR rate was 46% (n=82).

2. No ribavirin group: TPV 12 weeks/PEG-INF 12 weeks: SVR rate was 36% (n=78).

3. TPV 12 weeks/ RBV& PEG-INF 12 weeks: SVR rate was 60% (n=82).

4. TPV 12 weeks/ RBV &PEG-INF 24 weeks: SVR rate was 69% (n=81).

The PROVE 2 trial showed the importance of ribavirin, and the higher SVR rates with triple therapy of RBV/PEG-INF/TPV. However, more study was needed on patients with cirrhosis and patients who have previously failed treatment. Also, 5% of patients in this study were discharged because of severity of rash. Pruritis and rash need to be monitored closely in future trials.

The PROVE 3 TPV trial was a randomized, double blind, placebo-controlled phase II study. The participants had previously been treated with PEG-INF/RBV and failed either because of

null response or relapse. Patients were enrolled at 53 international sites, were between 18 and 70 years old with chronic HCV genotype 1. SVR in this study is defined as an undetectable HCV RNA level 24 weeks after the last dose of study drug (McHutchison et al. 2010). There were four arms to the study:

1. Control: PEG-INF/RBV for 48 weeks: SVR rate of 14% (n=114).

2. No ribavirin: TPV/PEG-INF 24/ PEG-INF 24: SVR rate of 24% (n=111).

3. TPV/PEG-INF/RBV for 12 weeks/ PEG-INF & RBV for 24 weeks: SVR rate of 51% (n=115).

4. TPV/PEG-INF/RBV for 24 weeks/ PEG-INF/RBV for 24 weeks: SVR rate of 53% (n=113).

This trial demonstrated that TPV given with PEG-INF/RBV is significantly more effective than PEG-INF/RBV alone and, again, that ribavirin is essential to HCV therapy (McHutchison, et al. 2011). The results of this trial should be interpreted with caution for those of Hispanic, African American or Asian decent as there were few of these patients included in this study (McHutchison et al. 2010).

Notable phase III trials for TPV include ADVANCE, REALIZE and ILLUMINATE. These trials showed that TPV/PEG-INF/RBV combination therapy is safe and significantly more effective at attaining a higher SVR rate in hepatitis C genotype 1 patients, both treatment naive and treatment failure patients, than the current standard of care therapy of PEG-INF /RBV alone (Patel et al. 2011).

In the phase III ADVANCE trial TPV was given with PEG-INF/RBV and was compared to PEG-INF/RBV alone for efficacy and safety. This was a randomized, double-blind and placebo-

controlled trial with 1088 HCV genotype 1 treatment naïve patients. Response guided therapy (RGT) was also evaluated and patients who achieved an early rapid virologic response (eRVR) were given shorter treatment times. Early rapid virologic response is defined as non-detectable serum HCV RNA at weeks 4 – 12. All of the patients in both telaprevir arms and the control arm were tested for HCV RNA levels at weeks 4 through 12.

1. The control arm (n=365): 48 weeks of PEG-INF/RBV only.

2. The second arm (n=365): 8 weeks of TPV/PEG-INF/RBV followed by 16 weeks of PEG-INF/RBV. If there was an eRVR, treatment time ended at 24 weeks. If not, then another 24 weeks of PEG-INF/RBV was given.

3. The third arm (n=365): 12 weeks of TPV/PEG-INF/RBV followed by 12 weeks of PEG-INF/RBV. If there was an eRVR, treatment time ended at 24 weeks. If not, then another 24 weeks of PEG-INF/RBV was given.

Those who had undetectable HCV levels at weeks 4 and12 were considered eRVR, and were eligible to discontinue therapy at 24 weeks. All other participants had extended therapy out to 48 weeks. Both TPV arms were superior to the control arm with SVR rates of 75% and 69% for 12 and 8 weeks of TPR respectively vs. 44% for the control group. The relapse rates at 24 weeks post therapy in the TPV arms was much lower at 8%, than in the control arm at 28% (Patel et al. 2011).

The ILLUMINATE trial was designed to determine if TPV can be given in a response guided therapy (RGT) manner with less treatment time for an early virologic response. Early significant drops in HCV RNA have been shown to be positive indicators for SVR rates

(Bisceglie, 2011). This was a randomized, double blind non-inferiority trial with 540 treatment naïve, HCV genotype 1 patients.

All patients received TPV for the initial 12 weeks. The three arms of the trial were defined, in part, by the patients' serum HCV RNA level. Early virologic response was defined as undetectable HCV RNA at weeks 4 and 12, and 352 (65%) of patients achieved this (Sherman, et al. 2011). These levels determined the different lengths of time PEG-INF alfa2a/RBV were given.

After the initial 12 weeks of treatment, those who had an eRVR by weeks 4 to 8 were divided into two groups: those who received 12 more weeks of PEG-INF/RBV (n=162) and those who received 36 more weeks of PEG-INF/ RBV (n=160). Those who did not achieve an eRVR went on to another 36 weeks of treatment with PEG-INF/RBV (n=118). The SVR rates were 92, 88 and 64 percent respectively. Thus, in those patients with an eRVR, the treatment regimen can be reduced to a total of 24 weeks with comparable outcomes to longer courses (Hoffman and Zeuzem, 2011).

In the ILLUMINATE trial, the Caucasian group had an overall SVR of 74%, while the latino (54 patients) and African American (73 patients) groups had SVR rates of 72 and 60 %, respectively. Participants with cirrhosis were not well represented in this trial, making up approximately 10% of the study population. Most patients had no fibrosis to portal fibrosis.

The randomized, placebo, phase III REALIZE TPV trial focused on HCV genotype 1 patients who had previously failed PEG-INF /RBV therapy. The participants in this study were relapsers, partial responders and null responders.

Results showed the TPV treated patients had significantly higher SVR rates than the control group with overall SVR rates for this study 64% to 66% in the TPV based arms and 17% in the control arm (Hofmann and Zeuzem, 2011). The REALIZE study showed TPV to be effective for prior HCV treatment failure patients.

Boceprevir

Boceprevir (BCE) has not been as studied, as much as telaprevir, but trials have shown it to be significantly more effective then PEG-INF/RBV alone, and safe for patients with chronic HCV genotype 1. It is not effective for other HCV genotypes.

SPRINT 1 was a phase II BCE trial on 520 treatment naïve patients with genotype 1 chronic HCV. The goal of this trial was to show the safety and efficacy of boceprevir as well as to evaluate low vs. high dose ribavirin in combination therapy (Feret, 2011). There were two parts and a total of seven groups in this trial. The first five groups:

1. Control: PEG-INF/RBV for 48 weeks (n=104).

2. PEG-INF/RBV for 4 weeks, followed by PEG-INF/RBV/BCE for 24 weeks (n=103)

3. PEG-INF/RBV for 4 weeks, followed by PEG-INF/RBV/BCE for 44 weeks (n=103).

4. PEG-INF/RBV/BCE for 28 weeks (n=107).

5. PEG-INF/RBV/BCE for 48 weeks (n=103)

The second part of the trial had two groups, evaluating ribavirin, as follows:

1. PEG-INF/RBV dose for weight /BCE for 48 weeks (n=16)

2. PEG-INF/RBV low dose (400-1,000mg./ day)/BCE for 48 weeks (n= 59).

As discussed by Feret (2011), the poorest results of the trial were in the control group which had a 38% SVR rate. The boceprevir treated patients sustained a significantly higher SVR rate than the control. The best results were in the group with the 4 week lead in, the

PEG/INF/RBV group that lasted 48 weeks. This group had an SVR of 75%. The higher dose ribavirin group had better results than the lower dose group with SVR rates of 50% vs. 36% respectively.

SPRINT 2 was a randomized, double blind, placebo controlled trial of BCE in which participants were treatment naïve genotype 1 HCV patients assigned to one of three groups (Poordad et al. 2011). The goal of this trial was to evaluate the safety and efficacy of BCE as an adjunct to PEG-INF alfa and RBV combination therapy. In addition, 24 weeks of BCE therapy was compared to 44 weeks in a response guided therapy manner.

There were three groups in the trial and a total of 1197 participants. All three had a lead in phase of PEG-INF/RBV for 4 weeks. The three groups were as follows:

1. Control group: PEG-INF/RBV for 4 weeks; PEG-INF/RBV/Placebo for 44 weeks (n=311).

2. Group 2: PEG-INF/RBV for 4 weeks; BCE plus PEG-INF/RBV for 24 weeks. Those with a detectable HCV RNA between weeks 8 and 24 were given placebo/PEG-INF/RBV for an additional 20 weeks (n=316).

3. Group 3: PEG-INF/RBV for 4 weeks; BCE/PEG-INF/RBV for 44 weeks (n=311).

Those with no detectable HCV RNA by week 8 were given a shorter treatment time of 28 weeks. All others received 48 weeks of therapy.

In the SPRINT 2 trials, the best response rates were in the BCE/PEG-INF/RBV with 44 weeks of BCE. The overall SVR rates were 66%, 63% and 37% for the BCE/PEG-INF/ RBV for 44 weeks; BCE/PEG-INF/RBV for 24 weeks; placebo/PEG-INF/RBV for 44 weeks respectively (Poordad et al. 2011).

African Americans have been shown to respond less favorably as a group to HCV anti-viral therapy (Hofman and Zeuzem, 2011). They were analyzed as a sub group in the SPRINT 2 trial. The SVR rates of this sub group were 53%, 42% and 23% compared to non-black patients whose SVR rates were 68%, 67% and 40% for the following groups: group 3, group 2 and the control group 1 respectively (Poordad et al. 2011).

The RESPOND 2 phase III BCE randomized, double blind and placebo controlled trial looked at patients with chronic hepatitis C genotype 1, who had previously received treatment with PEG-INF/RBV and failed by either partially responding or by relapsing within 24 weeks after completion of therapy (Feret, 2011). The study was looking at SVR rates in BCE/PEG-INF/RBV treated patients vs. PEG-INF/RBV treated patients.

Within the three arms of the trial, all arms received a 4-week lead in of PEG-INF/RBV before starting either BCE or placebo. The control arm was given 44 weeks of placebo after the lead in. Arm two was given 32 weeks of BCE after the lead in, with the option of an additional 12 weeks of BCE if there was a detectable HCV RNA at week 8 or anytime later. Arm three was given a total of 44 weeks of BCE/RBV/PEG-INF after the lead in.

The best SVR rate was found in arm 3 at up to 75% (Bacon, B. et al. 2011). The SVR rates in arm 2 were 59% in those who responded early and 21% in those who went on to receive the extra 12 weeks of BCE. In the control arm SVR rates were at 21%. Relapsers had a better response than did partial responders with rates of 75% and 69% respectively in the 44 week BCV/48 week PEG-INF &RBV arm (Hofmann & Zeuzem, 2011). No null responders to PEG-INF/RBV therapy were enrolled in this study.

Side Effects and Drug Interactions

Side effects in both the TPV and BCE trials were numerous and some, such as anemia and rash, led to therapy discontinuation. The vast majority of patients treated for HCV experienced some side effect. These commonly include nausea, neutropenia, thrombocytopenia, rash, anemia, fatigue, depression, anxiety and flu-like symptoms. Fatigue is the most common and increases in intensity as the treatment progresses (Tai & Chung, 2011).

In the ILLUMINATE trial of TPV 39% of participants experienced anemia and 44% experienced rash. Discontinuation of therapy because of anemia or rash occurred in 2% and 7% of the participants, respectively (Hofmann and Zeuzem, 2011).

The three PROVE trials (n=755) for TPV showed rash or anemia to be the most frequent side effects leading to discontinuation of therapy. Rash led to discontinuation in between 6.5 to 12 % of the patients. Anemia led to discontinuation for 0.8 to 2% of the participants (Patel et al, 2011). The manufacturers of TPV recommend that if the rash progresses to a severe level or if systemic symptoms develop TPR be discontinued (Incivek, 2011).

In 2010, a case report done by Montaudie, Passeron, Leccia, Sebbag and Lacour, published in Dermatology, describes a possible Drug Rash with Eosinophillia and Systemic Symptoms (DRESS) reaction to TPV of a patient enrolled in the PROVE studies.

The three PROVE studies showed a high frequency of cutaneous side effects and medication discontinuation because of rash, however, these side effects are not precisely described in the literature and are identified simply as pruritis and rash (Montaudie et al, 2010).

Because of the high incidence of rash in the TPV studies, further investigation and treatment protocols were incorporated into the drugs development. The FDA advisory committee briefing document (2011) on TPV states that a dermatology expert panel (DEP)

judged the rashes during the PROVE trials to be indistinguishable from those seen with the PEG-INF/RBV administration.

The dermatology expert panel judged the TPV rash to not be consistent with a life threatening hypersensitivity or anaphylactic reaction but to be mainly eczematous and pruritic in nature and covering less than 30% of the body. Pooled data from both phase 2 and 3 trials of TPV showed the vast majority of patients, 77%, were prescribed something for the rash. Typically steroid cream and antihistamines, but also oral steroids were prescribed (Patel et al. 2011).

Besides rash, anemia is the other common and potentially serious adverse effect of TPV administration. Anemia is a known side effect of PEG-INF/ RBV therapy, however, in conjunction with TPV this problem becomes compounded. During the phase II and III studies of TPV, the rate of anemia was shown to be double in the TPV/PEG-INF/RBV group when compared to the Placebo/PEG-INF/RBV group (Antiviral Drugs Advisory Committee Briefing, 2011). The cause of the anemia is thought to be that of myelosupression and hemolytic anemia from PEG-INF and ribavirin, respectively. The mechanism by which telapravir causes anemia is not completely understood. Management of drug related anemia includes monitoring of labs, reduction in ribavirin doses, transfusion, erythropoiesis-stimulating agents and therapy discontinuation.

The SPRINT and RESPOND trials produced data regarding the safety and efficacy of BCE. Overall, 98% of all patients involved in the BCE trials experienced some adverse effect (Feret, 2011). Most common problems were fatigue, headache and nausea in order of greater to lesser frequency. Anemia and neutropenia were two of the most significant side effects which required close monitoring and treatment or therapy discontinuation.

As discussed by Feret (2011), anemia (defined as a hemoglobin of less than 10 g/dL) occurred in roughly 50% of the BCE participants and was treated with erythropoiesis stimulating agents or ribavirin dose adjustment as recommended by the manufacturer. By comparison, the RBV/ PEG-INF only participants had rates of anemia that were 29%. The anemia usually started around the 4th week of treatment with BCE and reversed after treatment completion.

Adverse drug interactions were noted with BCE and several other medications. BCE is considered a strong inhibitor of the cytochrome P450 3A4 and 3A5, thus any medications that are metabolized through the 3A3/ 3A5 may have toxic increased plasma concentrations of the drug (Feret, 2011).

Significant interactions include those with the following drugs: statins, anti-seizure medications, anti-fungals, warfarin, ethinyl estradiol, carbamazepine, triazolam, drospirenone, calcium channel blockers, trazadone, alprazolam, clarithromycin, dihydropyridine, the phosphodiesterase type 5 inhibitors and cyclosporin (Feret, 2011).

Of note is that cyclosporin is a drug commonly given to liver transplant patients as an immunosuppressant agent, and that a common reason for liver transplantation is chronic HCV infection (Charlton, 2011). TPV is also categorized as an inhibitor of CYP3A and as such has similar drug interactions to BCE (Patel et al. 2011).

<center>Significance to Nurse Practitioners</center>

The role of the family practice nurse practitioner is twofold. First, one must understand the often silent and progressive nature of HCV, and second to know the standard of care for treatment of HCV in all genotypes. As mentioned earlier, the largest numbers of those infected with HCV contracted the disease in the 1980's. These are the people who will be seeking out the new therapies today. Family nurse practitioners should expect to see in their practices patients

receiving these medications from infectious disease specialists, and so it is important to understand the side effects of the medications as well as the interactions with other drugs in order to ensure safe care.

Discussion

The two new protease inhibitors boceprevir and telaprevir have become an addition to the combination drug standard of care for treatment of hepatitis C virus genotype 1. They are to be given always in combination with pegylated interferon alfa and ribavirin to avoid viral resistance and for better outcomes. These new drugs have been shown to significantly raise the sustained virologic response rate in both treatment naïve and prior treatment failure patients.

There are, however, significant drug-drug interactions and side effects that will necessitate close patient monitoring, treatment and potential drug discontinuation.

There are currently no head to head trials of these two protease inhibitors for HCV genotype 1, and this could be an area of future research. An area of future interest is the further study of sub groups, such as African Americans and Latinos with HCV.

References

Aberg, J., Goldman, M., Gray, L., Long, J. (2006). Infectious Diseases Handbook, 6th Ed. Lexi-Comp 1100 Terex Rd., Hudson, OH 44236.

Antiviral Drugs Advisory Committee Briefing Document NDA 201-917. Telaprevir 375mg. film coated tablet for the treatment of genotype 1 chronic hepatitis C. Available at ww.fda.gov.

Ashfaq, U., Javed, T., Rehman, S., Nawaz, Z., Riazuddin, S. An overview of HCV molecular biology, replication and immune responses. 2011. Virology Journal 2011,8:161.

Bacon, B., Gordon, S., Lawitz, E., Marcellin, P., Vierling, J., Zeuzem, M. et al. (2011). Boceprevir for previously treated chronic HCV genotype 1 infection. The New England Journal of Medicine. 2011 Mar 31;364(13): 1207-17.

Bisceglie, M. (2011). Response-guided therapy for chronic hepatitis C virus infection. Up To Date.com.

Charlton, M. (2011). Telaprevir, Boceprevir, Cytochrome P450 and Immunosuppressive Agents - A Potentially Lethal Cocktail. Hepatology: 2011; July.

Dipiro, J., Talbert, R., Yee, G., Matzkee, G., Wells, B., Posey, L. (2008) Pharmacotherapy: A Pathophysiologic Approach, 7th Ed. McGraw Hill Medical, New York.

Feld, J., Hoofnagle, J. (2005) Mechanism of action of interferon and ribavirin in treatment of hepatitis C. Nature: Vol. 436; August 18.

Fensterl, V., Sen, G. (2009). Interferons and Viral Infections. Biofactors 35 (1): pp.14-20.

Feret, B. (2011). Boceprevir: A new oral protease inhibitor for the treatment of chronic hepatitis C. Formulary. 2011; September Vol. 46.

Ghany, M., Nelson, D., Strader, D., Thomas, D., Seeff, L. (2011). An Update on Treatment of Genontype 1 Hepatitis C Virus Infection: Practice Guideline by the American Association for the Study of Liver Diseases. Hepatology Vol. 54 No. 4.

Hézode C, Forestier N, Dusheiko G, et al. (2009). Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. N Engl J Med 2009; 360:1839.

Hofman, W., Zeuzem, S. (2011). A New Standard of Care for the Treatment of Chronic HCV Infection. Nature Reviews. May 2011, Volume 8.

Incivek [package insert]. (2011). Cambridge MA: Vertex Pharmaceuticals Incorporated; 2011. Jacobson, I. McHutchinson J. Dusheiko, G. et al. Telaprevir for previously treated chronic HCV infection. New England Journal of Medicine; 364:2405.

Kieffer, T., Sarrazin, C., Miller, J., Welker, M., Forestier, N., Reesink, H. (2007) Telaprevir and pegylated interferon-alfa-2a inhibit wild-type and resistant genotype 1 hepatitis C virus replication in patients. Hepatology:46(3) pp.631-639.

Lang, L. (2007) Interim Results Presented at EASL From PROVE 1 Clinical Trial of Investigational Drug Telaprevir in Patients with Genotype 1 Hepatitis C. Gastroenterology; Vol.132: 7. Pp. 2283-2284.

McHutchison, J., Manns, M., Muir, A., Terrault, N., Jacobson, I., Nezam, H. et al (2010). Telaprevir for Previously Treated Chronic HCV Infection. New England Journal of Medicine: 362;14 pp. 12921303.

Montudie, H., Passeron, T., Cardot-Leccia, N., Sebbag, N., Lacour, J. (2010). Drug Rash with Eosinophilia and Systemic Symptoms due to Telaprevir. Dermatology. 2010;221:303-305.

Morikawa, K., Lange, C., Gouttenoire, J., Meylan, E., Rass, V., Penin, F. et al. (2011).

Nonstructural protein 3-4A: the Swiss army knife of hepatitis C virus. Journal of Viral Hepatology. 2011; May;18(5):305-15.

Patel, K., Pauli, M., Abdelghany, S.(2011). Telaprevir: A novel, protease inhibitor for the treatment of hepatitis C virus. Formulary 2011; June Vol. 46.

Pearlman, B. (2011). Hepatitis C. Epocrates online.com

Poordad, M., McCone, J., Bacon, B., Bruno, S., Manns, M., Sulkowski, M. (2011). Boceprevir for Untreated Chronic HCV Genotype 1 Infection. The New England Journal of Medicine. 2011: Vol: 364 No. 13.

Sanjiv, C.(2011). Extrahepatic manifestations of hepatitis C virus infection. 2011. Up to Date.com.

Sharma, S. (2010). Hepatitis C virus: Molecular biology and current therapeutic options. 2010. Indian Journal of Medical Res. Vol.:131, January 2010. pp. 17-34.

Sherman, K., Flamm, S., Afdhal, N., Nelson, D., Sulkowski, M., Everson, G. et al (2011). Response Guided Telaprevir Combination Treatment for Hepatitis C Virus Infection. The New England Journal of Medicine 2011: Vol: 365;11. pp1014-24.

Tai, A., Chung, R. (2011). Telaprevir and boceprevir in the treatment of chronic hepatitis C virus genotype 1. 2011. Up to Date.com.

Turkoski, B., Lance, B., Tomsik, E. (2009). Drug Information Handbook for Advanced Practice Nursing 10th Ed. 2009. Lexi-Comp: Hudson, Ohio 44236.

Wyles, D. (2010). Moving Beyond Interferon Alpha: Investigational Drugs for Hepatitis C virus Infection. Topics in HIV Medicine. 2010.Vol.:18 (4). pp.132-136.